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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/583,508	GUSTAVSSON ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☒ Claim(s) *20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/16/2006 and 9/18/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-23 are presented for examination

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-13, in the reply filed on 3/26/2009 is acknowledged. The traversal is on the ground(s) that the Examiner has not provided any comments as to how WO 91/17660 teaches or suggests each and every feature of the invention as defined by the claims of Groups I-IV or the species election of compounds encompassed by the genus "multi-targeting antifolate" as recited in claims 1, 8, 14, and 17. Applicants argue that without this information they cannot properly respond to the Restriction Requirement. This argument is found persuasive because Applicants define "multi-targeting antifolate" to mean an antifolate which acts on two or more of the enzymes involved in folate synthesis (page 14, lines 24-27). 5-Fluorouracil is only known to inhibit one such enzyme, thymidate synthase, and thus appears to not be within the scope of Applicant's claimed invention.

Accordingly, the Restriction Requirement between Groups I, II, III, and IV as set forth in the Office Action dated 2/26/2009 is hereby **withdrawn** and claims 1-23 are under examination.

Applicant's election of the multi-targeting antifolate specie pemetrexed in the reply filed on 3/26/2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Priority

This application is a 371 of PCT/SE2004/001955, filed December 24, 2004, and claims foreign priority under 35 U.S.C. 119(a)-(d) or 365(b) to Swedish Application 0303526-8, filed 12/22/2003.

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statements filed 6/16/2006 and 9/18/2008. The Examiner has considered the references cited therein to the extent that each is a proper citation. Please see the attached USPTO Form 1449.

Claim Objections

Claim 20 is objected to because of the following informalities: the word "chemoterapeutic" is misspelled in line 2. The correct spelling is ---chemotherapeutic--- as found elsewhere in the claims and specification. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-7 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112 – 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 provides for the use of at least one of tetrahydrofolate, methylene-tetrahydrofolate, and methyl-tetrahydrofolate, and at least one multi-targeting antifolate, for the

manufacture of a medicament, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 1-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Independent claims 1, 8, 14, and 17 recite the limitation "...at least one of tetrahydrofolate, methylene-tetrahydrofolate and methyl-tetrahydrofolate...". In the absence of a comma between methylene-tetrahydrofolate and methyl-tetrahydrofolate, it is unclear whether the "at least one of" refers to 1) tetrahydrofolate **or** 2) methylene-tetrahydrofolate and methyl-tetrahydrofolate, or whether "at least one of" refers to 1) tetrahydrofolate and/or 2) methylene-tetrahydrofolate and/**or** 3) methyl-tetrahydrofolate.

Claims 2 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 2 and 9 recite the abbreviation "THF", but do not precede this abbreviation with the full meaning of the abbreviated term. As such, the claims are unclear with respect to what "THF" is intended to mean. For example, "THF" could be interpreted to mean the solvent, tetrahydrofuran.

Claims 2 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 2 and 9 recite the limitation "said THF, methyl-THF and/or methylene-THF" in line 2 of claim 2 and lines 2 and 3 of claim 9. There is insufficient antecedent basis for this limitation in the claim.

Claims 6 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite the limitation "...common pharmaceutical

composition". The metes and bounds of the claims are unclear because it is not apparent whether "common pharmaceutical composition" is to be given its ordinary meaning, i.e., that tetrahydrofolate and a multi-targeting antifolate are formulated in a widespread or general pharmaceutical composition, or whether Applicants mean that the tetrahydrofolate and multi-targeting antifolate are formulated together in the same composition.

Claim Rejections - 35 USC § 112 – 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 4-9, 11-18, and 20-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1st "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are drawn to compositions and methods comprising at least one of tetrahydrofolate, methylene-tetrahydrofolate and methyl-tetrahydrofolate, and at least one "multi-targeting antifolate". Other than pemetrexed, ralitrexed, and lometrexol, the disclosure lacks adequate written description of the claimed "multi-targeting antifolate".

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claims indicates that these claims are drawn to a generic genus, *i.e.*, generic multi-targeting antifolate compounds.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(i), the court states, "An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

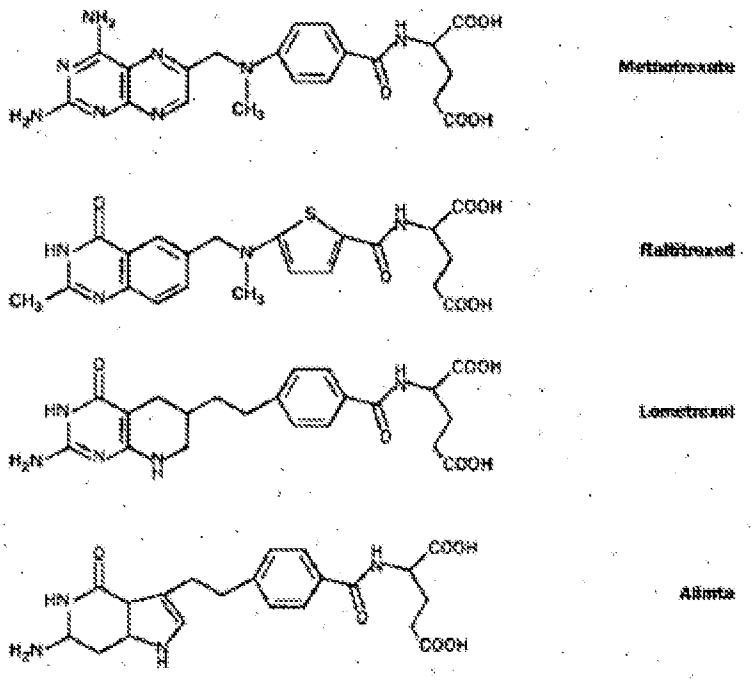
The specification discloses that multi-targeting antifolates may be selected from the group consisting of premetrexed [*sic* – pemetrexed], raltitrexed, and lometrexol (page 4, lines 28-30; page 15, lines 3-6).

The specification further discloses that “other multi-targeting antifolates, as well as other substances which possess the characteristics of multi-targeting antifolates may be used" (page 4, lines 30-33).

The specification discloses that the term "multi-targeting antifolate" (or "multi- functional antifolate") as used in the present application relates to an antifolate which acts on two or more of the enzymes involved in folate synthesis.

The specification discloses three structurally related species that are within the scope of the claimed genus, *i.e.* pemetrexed, ralitrexed, and lometrexol. The structures of these agents, along with methotrexate, are reproduced below for ease of discussion (reproduced from Curtin et

al. (The Lancet, May 2001, vol. 2, page 300, Figure 3). Note that "Alimta" is the trade name of pemetrexed (see instant specification at page 15, lines 4-5).



The multi-targeting antifolates disclosed by Applicants are structurally related to one another, as well as to the single-targeting antifolate, methotrexate. It is not clear from the prior art or Applicant's disclosure what specific structural features are necessary for such compounds to target multiple enzymes involved in folate synthesis, rather than only one enzyme such as seen with methotrexate. As such, based on Applicant's disclosure, one skilled in the art would not know what compounds, other than pemetrexed, raltitrexed, and lometrexol, are multi-targeting antifolates as recited in the instant claims. It is noted that the prior art appears to recognize pemetrexed as a "multitargeted antifolate". For example, a search of MEDLINE with the term "multitargeted antifolate" results in identification of articles describing pemetrexed, but not other compounds. A similar search in MEDLINE with the term used by Applicants, "multi-targeting antifolate", results in no prior art. As such, it is apparent that "multi-targeting antifolate" is not a term used in the art to describe compounds that inhibit more than one enzyme involved in folate synthesis.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus, which is a generic genus of

compounds, *i.e.*, generic multi-targeting antifolate compounds purported to have anticancer activity. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the claimed genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claims 17-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of cancer to the extent that "treatment" refers to alleviating the symptoms of cancer, does not reasonably provide enablement for the treatment of cancer to the extent that "treatment" refers to a cure or prevention of cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This is a Scope of Enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to the "treatment" of cancer in a patient comprising administration to the patient at least one of tetrahydrofolate, methylene-tetrahydrofolate and methyl-tetrahydrofolate, and at least one multi-targeting antifolate (e.g., pemetrexed). Pursuant to Applicant's explicit definition of "treatment", the term "treatment" as used in the present specification and claims relates to both treatment in order to **cure** or alleviate the symptoms of cancer, and to treatment in order to **prevent the development of cancer** (page 15, lines 20-25). The claimed method thus encompasses curing and preventing cancer in a patient.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable

factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain).

It is well established in the art of oncology that cancer cannot be "cured" or "prevented". Despite decades of scientific research and experimentation, there are presently no known cures for cancer, nor are there any chemical agents capable of preventing cancer in patients. While treating cancer, for example by slowing tumor growth, alleviating symptoms of cancer, inducing cancer cell death, etc. are well known in the art, cancer reoccurrence is commonplace. As such, the idea of a "cure" for cancer goes against established medical science. Similarly, because of the numerous undefined causes of cancer, the idea that one can prevent cancer generally in a patient also goes against established medical science. For example, while there are many chemotherapeutic agents routinely used to treat cancer, there is no established method of generally preventing cancer from occurring.

2. The breadth of the claims

The claims vary in breadth; some (such as claim 17) vary broadly, reciting the treatment of cancer with at least one of tetrahydrofolate, methylene-tetrahydrofolate and methyl-tetrahydrofolate, and at least one multi-targeting antifolate. Others, such as claims 19 and 23, are narrower, reciting specific species of the claimed multi-targeting antifolate (claim 19) or specific types of cancer (claim 23). All, however, are extremely broad insofar as they disclose the general "treatment" of cancer in a patient comprising administration of the same compounds. As discussed supra, such "treatment" encompasses both curing and preventing cancer.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification discloses methods of treating cancer comprising administration of at least one of tetrahydrofolate, methylene-tetrahydrofolate and methyl-tetrahydrofolate, and at least one multi-targeting antifolate, optionally in further combination with at least one chemotherapeutic agent (page 6, lines 10-20).

The specification discloses that the term "pharmaceutically active amount" as recited in the instant claims relates to a dose of a substance that will cure or alleviate the symptoms of different types of cancer or prevent the development of cancer (page 15, lines 26-32).

The specification discloses that THF, methylene-THF, and/or methyl-THF, and the multi-targeting antifolate, may be administered simultaneously or consecutively (page 15, lines 33-35). The specification further discloses that the order in which drugs and folate are administered could be of major importance for the outcome of chemotherapeutic treatment (page 16, lines 18-20).

The specification discloses that THF, methylene-THF, and/or methyl-THF are preferably administered in a dose of 100 mg to 1000 mg, preferably 100-200 mg, corresponding to approximately 1-5 mg/kg of body weight (page 17, lines 10-15) which may be administered daily, weekly, or monthly (id. at lines 16-17) subcutaneously, intramuscularly, intravenously, intraarterially, intraperitoneally, intranasally, or orally (id. at lines 17-19).

The specification does not disclose doses of the claimed multi-targeting antifolates.

The working examples are limited to administration of pemetrexed in combination with methylene-tetrahydrofolate to rats bearing an experimental adenocarcinoma (Example 2). Figure 5 shows that the tumor remained (i.e., was not "cured") after treatment.

The specification thus provides no direction or guidance for determining the particular administration regimens (*e.g.*, dosages, timing, administration routes, etc.) necessary to cure or prevent all of the various cancers claimed, particularly in humans. There is one *in vivo* assay described in Example 2, but it it is unclear if this treatment assay is predictive of curing or preventing cancer as encompassed by the claims. There is no working example of curing or preventing any cancer in animals or man.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly combination of compounds could be predictably used as a cure or prevention for all cancers as inferred in the claims and contemplated by the specification.

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

In the instant case, Applicants have presented a general idea that because a combination of pemetrexed and methylene-tetrahydrofuran inhibits adenocarcinoma tumor growth the combination must therefore, *a priori*, be useful in curing or preventing cancer in a patient. However, curing and/or preventing cancer with chemotherapeutic agents go against established medical science as discussed supra. While there are numerous single agents and combinations of agents effective in inhibiting tumor growth in vivo, there are no known cures or preventions of cancer.

Determining if any particular claimed combination would cure or prevent any particular cancerous disease state would require hit-or-miss testing to determine effective doses, administration routes, and administration regimens in clinical trials or in testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by Applicants.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

> such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over **WO 91/17660** (Published November 28, 1991) (cited on IDS filed 6/16/2006) in view of **Hanauske *et al.*** (The Oncologist, 2001, vol. 6, pages 363-373) (newly cited) and **Niyikiza *et al.*** (Molecular Cancer Therapeutics, May 2002, vol. 1, pages 545-552) (cited on IDS filed 6/16/2006).

The instant claims are drawn to compositions and kits comprising at least one of tetrahydrofolate, methylene-tetrahydrofolate and methyl-tetrahydrofolate, and at least one multi-targeting antifolate, optionally in further combination with at least one chemotherapeutic agent as well as methods of treating cancer comprising administration of at least one of tetrahydrofolate, methylene-tetrahydrofolate and methyl-tetrahydrofolate, and at least one multi-targeting antifolate, optionally in further combination with at least one chemotherapeutic agent.

WO '660 teaches 5,10-methylene-tetrahydrofolate (CH_2FH_4) and its solution isomer FH_4 (tetrahydrofolate) as modulators of the *in vivo* antitumor effects of the antifolate 5-fluorouracil (Abstract; page 1, lines 5-13). The therapeutic mechanism of 5-fluorouracil against colon cancer cells is disclosed to be complete inhibition of thymidylate synthase (TS) or abrogation of TS activity (page 1, lines 23-29). CH_2FH_4 (*i.e.*, methylene-tetrahydrofolate) is a normal intracellular metabolite of the B-vitamin, folic acid, for use in thymidylate synthesis by TS (page 4, lines 23-25). The inventors disclose compositions and methods comprising CH_2FH_4 or FH_4 and 5-fluorouracil for the treatment of cancer (page 10, lines 8-17). The CH_2FH_4 or FH_4 may be administered concurrently with 5-fluorouracil or prior to the administration of 5-fluorouracil as recited in claims 21 and 22 (page 10, lines 12-14). The CH_2FH_4 or FH_4 can be administered as

the biologically active isomers as recited in claims 2, 9, 15, and 18 (page 11, lines 6-8; page 18, lines 6-16). WO '660 discloses that CH_2FH_4 of FH_4 can be used in a method to reduce the toxicity of "an anti-folate drug" which has been administered to a patient. Examples of such anti-folate drugs include methotrexate, trimetrexate, nitrous oxide, and dideoxytetrahydrofolic acid (page 11, lines 14-19; page 19, lines 7-22). Combination chemotherapy with additional chemotherapeutic agents as recited in claims 4, 11, 16, and 20 is disclosed at page 18, lines 17-33).

The instant claims differ from the disclosure of WO '660 in that the primary reference does not explicitly disclose combining methylene-tetrahydrofolate or tetrahydrofolate with a "multi-targeting antifolate" such as pemetrexed.

However, Hanauske *et al.* teach that pemetrexed is a novel antifolate clinically active against multiple solid tumors, including non-small cell lung cancer, breast, mesothelioma, colorectal, pancreatic, gastric, bladder, cervix, and head and neck (Abstract; pages 366-369; Table 3). Pemetrexed is a multi-targeting antifolate that inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR), glycinamide ribonucleotide formyltransferase (GARFT), and aminoimidazole carboxamide ribonucleotide formyltransferase (AIRCARFT) (Abstract; page 363, right column to page 364, left column; Figure 2). As taught in Hanauske *et al.*, it was known in the art that folic acid added to the diet in preclinical studies reduced the toxicities of pemetrexed while maintaining antitumor activity (Abstract). The authors further disclose that combining pemetrexed with other antitumor agents (*e.g.*, 5-fluorouracil or paclitaxel) results in a synergistic effect (page 365, left column). Similar additive or synergistic effects were obtained when pemetrexed was combined with gemcitabine, carboplatin, cisplatin, oxaliplatin, cyclophosphamide, or doxorubicin (page 365, left column). Also see pages 369 to 370 and Table 4. Preliminary studies have indicated that addition of folic acid ameliorates toxicities permitting dose escalation of pemetrexed (page 371, left column).

The primary and secondary references discussed above thus teach that CH_2FH_4 or FH_4 are useful in combination with 5-fluorouracil and other anti-folate drugs, that the multi-targeting antifolate pemetrexed was known in the art to be effective against multiple cancer types, both alone and in combination with other chemotherapeutic agents, and that addition of folic acid ameliorates toxicities of pemetrexed.

Niyikiza *et al.* is provided as further motivation to administer tetrahydrofolate, methylene-tetrahydrofolate, and/or methyl-tetrahydrofolate in combination with the multi-targeting antifolate pemetrexed. In this regard, Niyikiza *et al.* teach that high pretreatment levels of homocysteine and/or methylmalonic acid are predictive of severe toxicity associated with pemetrexed therapy (Abstract; pages 547-549; Figure 3). Based on this observed correlation, the authors suggest that by reducing homocysteine and/or methylmalonic acid levels (*e.g.*, by administration of folic acid), one could substantially reduce a patient's risk for severe toxicity while maintaining efficacy of the drug. The authors thus disclose a study of supplementation with folic acid and vitamin B_{12} for all patients participating in pemetrexed clinical trials. Such supplementation reduces homocysteine and, in turn, results in significant reduction of toxicity associated with pemetrexed therapy, while maintaining, or possibly improving, efficacy (page 551, right column).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to formulate compositions and kits comprising tetrahydrofolate, methylene-tetrahydrofolate, and/or methyl-tetrahydrofolate and pemetrexed and administer such a combination to a patient with cancer. The skilled artisan would have been motivated to do so because tetrahydrofolate, methylene-tetrahydrofolate, and methyl-tetrahydrofolate are known biologically active metabolites of folic acid (see WO '660; Figure 2 of Hanauske *et al.*; and Figure 1 of Niyikiza *et al.*). Because pemetrexed inhibits multiple enzymes responsible for conversion of folic acid to these compounds, and for the conversion of these compounds to one another, the skilled artisan would expect that administration of one or more of these compounds in combination with the multi-targeting antifolate pemetrexed would allow these compounds to elicit their biological activity without having to first be formed *in vivo* from folic acid or one another. Such is evidenced by WO '660, who teach administration of methylene-tetrahydrofolate or tetrahydrofolate rather than folic acid *per se* in combination with antifolate compounds. The skilled artisan would expect that if the methods disclosed in WO '660 are effective with antifolate compounds that target one enzyme, then they would also be effective with antifolate compounds that target multiple enzymes. This is especially true because pemetrexed inhibits the same enzyme (TS) as 5-fluorouracil. Furthermore, because methyl-tetrahydrofolate is involved in the conversion of homocysteine to methionine (see Figure 1 of

Niyikiza *et al.*), the skilled artisan would expect that administration of methyl-tetrahydrofolate would be effective in reducing homocysteine levels in patients undergoing pemetrexed therapy, which would be reasonably expected to reduce pemetrexed toxicity as discussed in Niyikiza *et al.*

With regard to claims 5 and 12, it would have been obvious to one of ordinary skill in the art that if the methylene-tetrahydroformate, methyl-tetrahydrofolate, and/or tetrahydrofolate are administered prior to or after the antifolate, that they would be formulated in different pharmaceutical compositions. Similarly, if the methylene-tetrahydroformate, methyl-tetrahydrofolate, and/or tetrahydrofolate are administered simultaneously with the antifolate, then they would be formulated in the same composition as recited in claims 6 and 13.

With regard to claims 14-16, kits comprising pharmaceutical agents are commonplace in the art. The skilled artisan would immediately recognize the benefit of providing pharmaceutical compositions in kits for ease of storage, transport, and administration to patients.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/James D Anderson/
Examiner, Art Unit 1614